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Embolus Prevention: Anticoagulant therapy in comparison to Watchman's procedure in patients with atrial fibrillation

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EMBOLUS PREVENTION: ANTICOAGULANT THERAPY IN COMPARISON TO WATCHMAN'S PROCEDURE IN PATIENTS WITH ATRIAL FIBRILLATION

By

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Abstract

Atrial fibrillation is a common cardiac disease that occurs as individuals age. One of the risk factors of atrial fibrillation is blood clot formation or embolus in the left atrium. Current treatment methods to prevent clot formation include a variety of anticoagulants, and left atrial appendage closure devices, specifically the relatively new Watchman's device, the only FDA approved left atrial appendage closure device. This literature review researched articles comparing the differences in both long-term anticoagulation therapy and Watchman's device for blood clot prevention. Study results confirm the rising efficacy and cost effectiveness of Watchman's device versus long term anticoagulant therapy as well as their adverse effects regarding placement and post procedure; however further randomized control trials are needed as mentioned by the authors referenced in this paper, comparing both therapies particularly novel oral anticoagulants head to head rather than through extrapolation. Long term effects of Watchman's device also need to be studied.

Keywords: atrial fibrillation, embolus, anticoagulant therapy, Watchman's device, left atrial appendage closure.

Embolus Prevention: Anticoagulant Therapy in Comparison to Watchman's Procedure in Patients with Atrial Fibrillation

Introduction

Anticoagulant therapy has been a mainstay treatment for patients who have atrial fibrillation or a-fib for prevention of blood clots. With routine use of an oral and or non-oral anticoagulants the patient's risk for developing a thrombus or embolus is markedly diminished. There are many risks involved by taking oral or non-oral anticoagulants: prolonged bleeding, increased bruising, hemorrhagic stroke, etc. Also, cost of continued therapy can become quite expensive. A relatively new procedure was introduced, in 2015 the FDA approved the Watchman's procedure. This procedure entails the insertion of a closure device into the left atrial appendage of the left atrium to block blood clots before they exit due to a-fib. The purpose of this study will be to review both long term anticoagulant therapy and the Watchman device as prophylactic treatments, as well as the difference between the two regarding their purpose, in addition to comparing their of costs, risks, and benefits.

Statement of the Problem

Patients who suffer from atrial fibrillation are at risk of developing an embolus which can cause a potential harming blockage in the body. Many patients who take anticoagulants run the risk of bleeding and increased costs due to appointments and medication refills. Watchman's device, a relatively new treatment in preventing embolus or blood clots in the heart, needs to be considered for patients who suffer from atrial fibrillation.

Research Questions

For prevention of embolus formation from atrial fibrillation in the adult and older adult population, would anticoagulant therapy or Watchman procedure be a better choice?

When comparing Watchman's procedure and long-term anti-coagulant therapy for eligible patients, which choice would be the best economically for the patient?

Methodology

For the following review, the author searched multiple databases to gather research including Cochrane Database of Systematic Reviews, PubMed, DynaMed, UpToDate, Elsevier, Essential Evidence Plus, and guidelines from the American Heart Association, American College of Cardiology Heart Rhythm Society and European Society of Cardiology. Articles and studies chosen for review were published between the years 1999-2018, the articles chosen were peer reviewed and included systematic reviews, non-randomized cohort study, meta-analysis, and randomized control trials (RCTs). For this review, 19 resources were used. The research is based on human studies. Much of the research gathered describes Watchman's procedure, as well as why anticoagulant therapy is used for atrial fibrillation.

Keywords and MeSH terms: Atrial fibrillation, bleeding, LAA closure, left atrial appendage, watchman's procedure, device, stroke, percutaneous left atrial appendage closure, anticoagulant agent, NOACs, antithrombotic, antiplatelet therapy, randomized control trial, cardiac, cardiology, warfarin, apixaban, thromboembolic, aspirin, clopidogrel, cost effectiveness, aspirin

Literature Review

Atrial fibrillation or a-fib is a condition that effects many as they age and is the most common cardiac arrhythmia in the world (Markides & Schilling, 2003). In fact, it is so common, it affects 1% to 2% of the general population at large (Pellman, Sheikh, Diego, & Jolla, 2017). A-fib is seen more so in older adults and tends to affect this population the most. The prevalence and incidence of a-fib increases substantially after 65 years of age, and it is found in greater than 10% of patients once they reach the age 85 years (Boriani, 2016).

What is atrial fibrillation

The epidemiology of a-fib has many potential causes. It is thought to be caused mainly by a micro-reentry action potential, enhanced automaticity in the atria of the heart, or triggered activity of the heart (Markides & Schilling, 2003). When the electrical automaticity of the heart is affected by a-fib, the heart begins to fibrillate or contract in various areas of the atria, rather than produce a normal wave like contraction in a healthy heart. When this happens, the heart does not produce efficient enough contractions to move blood to the ventricles. Electrical abnormalities, structural alterations and other contributory effects contribute to a-fib incidence as well. Some structural alterations of the heart are known to be the cause of a-fib, including oxidative stress, inflammation, heart hypertrophy, and muscular fibrosis (Pellman, Sheikh, Diego, & Jolla, 2017). Alterations in structure of the heart can be associated with aging, environmental effects, or genetic abnormalities. Other contributory effects of a-fib can be seen with endocrine abnormalities e.g. thyroid, adrenal glands, and insulin insensitivity (Pellman, Sheikh, Diego, & Jolla, 2017).

By affecting the heart's automaticity or normal contraction, blood can become stationary or remain in the atria when the heart fibrillates for a long period of time. When blood enters the atria and becomes stagnant it not only affects cardiac and circulatory function, it can potentiate the risk of embolic stroke, pulmonary embolism, as well as worsening heart failure (Pellman, Sheikh, Diego, & Jolla, 2017). The potential damage caused by an ischemic stroke via embolus or detached blood clot in the brain averages 120 million neurons, 830 billion synapses, and 714 kg or 447 miles of myelinated fibers (Boriani, 2016). Due to a-fib, and the potential for subsequent thrombus or emboli formation, risk of stroke is automatically increased five-fold (Gutierrez & Blanchard, 2016).

Types and risk of A-fib

According to a study performed by Pellman, Sheikh, Diego, & Jolla (2017) there are many forms of a-fib that are clinically relevant. Some forms of a-fib include: a first detected episode in which a clinician observes a-fib in a clinical setting; a paroxysmal episode of a-fib, which only has one occurrence; persistent a-fib which converts to normal sinus rhythm after 7 days; and permanent a-fib which does not spontaneously convert to normal sinus rhythm (Pellman, Sheikh, Diego, & Jolla, 2017). The most common type of a-fib is non-valvular a-fib. Non-valvular a-fib spares the tricuspid valve as well as the mitral valve of any fibrillation and only affects areas around the left atria. Non-valvular causes of a-fib in any given population are seen in patients who have a history of myocardial infarct, ischemia, heart failure, post heart procedures, or congenital abnormalities (Pellman, Sheikh, Diego, & Jolla, 2017).

Who is at most risk for developing a-fib? The top risk factors that are associated with a-fib are as stated before are age as well as sex. As individuals age, risk of developing atrial fibrillation is doubled every decade (Pellman, Sheikh, Diego, & Jolla, 2017). Compared to

women, men have a higher risk of developing atrial fibrillation. Males have a 1.5 times risk of atrial fibrillation in their lifetime (Pellman, Sheikh, Diego, & Jolla, 2017).

Diagnosing A-fib

A systematic review by Guitierrez & Blanchard (2016) described the diagnostic criteria for a-fib. This article was for educational purposes for providers. In order to diagnose a-fib, a provider uses a 12-lead electrocardiogram or EKG in any setting with computer software. This combination shows sensitivity of 92% and a specificity of 91% to diagnose a-fib (Guitierrez & Blanchard, 2016). When reading an EKG that displays a-fib, the provider can see a loss of p-waves in a normal heart rhythm with the replacement of fibrillatory waves and an association with over-activity of the left and right ventricles leading to a rapid heart rate between 90 and 170 beats per-minute (Guitierrez & Blanchard, 2016). Without EKG, diagnosis of A-fib can be difficult. Some patients have some, if no symptoms including heart failure, myocardial infarction, stroke, or hemodynamic collapse. If a provider did not have an EKG available, measuring pulse rate alone to assess for a-fib can suffice. Pulse rate has a 94% sensitivity, but only a 72% specificity for diagnosis, with a positive likelihood ratio equaling 3.4; and a negative likelihood ratio = 0.08 (Guitierrez & Blanchard, 2016). Irregularity of beats is the main finding when measuring the pulse only and should not be used alone for diagnosis. If suspicion of A-fib occurs in a patient with a normal EKG, a Holter monitor or event monitor should be used for further study. These monitors allow patients to record 'events' that they notice e.g. chest pain, palpitations, headache, increased heart rate, etc. outside of medical institutions when they are currently doing daily activities of living (Guitierrez & Blanchard, 2016). As a provider, it is imperative to always perform a complete history and physical on patients who presents with chest pain, fatigue, dizziness, etc. as well as questioning prescription or illicit substance use to

rule out a-fib (Guitierrez & Blanchard, 2016). Additionally, laboratory tests can help to narrow the focus of diagnosing a-fib as well. Blood tests to consider when evaluating a patient and when considering a differential diagnosis would be: a complete blood count, comprehensive metabolic panel, thyroid stimulating hormone, as well as liver and kidney function tests (Guitierrez & Blanchard, 2016). Imaging to consider would be echocardiography and chest radiography. Further testing includes stress echocardiography via nuclear perfusion or cardiac catheterization and possibly a sleep study to rule out any decrease in oxygen consumption (Gutierrez & Blanchard, 2016).

Treating A-fib

According to Gutierrez & Blanchard (2016) who reviewed the current treatment of a-fib, a provider must keep several things in mind when approaching a-fib: how to control the heart's ventricular rate, the heart's ventricular rhythm, anticoagulant use for potential blood clots, and which medication to administer.

Ventricular rate is best controlled with a beta blocker or a non-dihydropyridine calcium channel blockers. These medications are contraindicated in certain patients who present with certain preexcitation syndromes, COPD, and asthma (Gutierrez & Blanchard, 2016).

Ventricular rhythm is mostly controlled by class Ic and IIIc antiarrhythmic drugs which are shown to be the most effective for arrhythmias. Each class affects different electrolyte channels of the heart. Class Ic antiarrhythmics exert effects on sodium channels to reduce the heart's action potential. Class IIIc antiarrhythmics exert their effects on potassium channels prolonging refractoriness and lengthening the QT interval of the heart, thus delaying conduction failure (Pellman, Sheikh, Diego, & Jolla, 2017).

Digoxin and amiodarone are used as adjuncts for treatment of a-fib or when beta blockers or calcium channel blockers fail, however they both possess harmful effects and narrow windows of treatment (Gutierrez & Blanchard, 2016). Despite this, amiodarone has been shown as the most effective agent for restoring sinus rhythm in patients with persistent atrial fibrillation showing restoration in 44% of patients at 2 days and 68% in nine months (Markides & Schilling, 2003). It should be kept in mind that amiodarone can potentiate the effects of anticoagulant drugs, increasing potential risks (Pellman, Sheikh, Diego, & Jolla, 2017). Restoration of sinus rhythm is associated with improvements in exercise capacity and peak oxygen use both in patients with heart disease and normal hearts (Markides & Schilling, 2003).

There are other forms of treating of a-fib to consider. When drug therapy fails, cardioversion can be used to treat a-fib. Treatment with cardioversion depends on patient status e.g. acute a-fib within 2 days, possible thrombi in patient, age, and drug interaction (Gutierrez & Blanchard, 2016). Ablation therapy is also a treatment and prevention for a-fib. Ablation therapy is indicated in patients who have a poor tolerance to antiarrhythmics from side effects or poor control with pharmacologic intervention (Pellman, Sheikh, Diego, & Jolla, 2017). Left atrial appendage (LAA) isolation made by Watchman's procedure is a surgical procedure which is another form of treating A-fib. The aim of LAA restriction is to reduce stroke risk by percutaneous ligation or removal of the LAA. LAA obliteration does not stop a-fib, it only walls off the appendage where 90% of cardiac thrombi occur due to blood pooling caused by Atrial fibrillation (Gutierrez & Blanchard, 2016).

Anticoagulant therapy

Markides & Schilling (2003) discussed how current medical practice prevents coagulation risk in patients with a-fib. This article assessed the current uses of anticoagulant

therapy for a-fib and its benefits. In general, decisions regarding anticoagulation therapy should be based on risk factors of thromboembolism: prior stroke, TIA, valvular or other heart disease, diabetes, age, cardiac function and other comorbidities of the patient (Markides & Schilling, 2003). The American College of Cardiology or ACC is the standard of reference for potential candidates for anticoagulant therapy. The ACC has created the $CHADS_2$ and CHA_2DS_2-VAS_C algorithms to help the provider determine the need of anticoagulant therapy (Markides & Schilling, 2003). $CHADS_2$ components include patient history of congestive heart failure, hypertension, age of 75 years or older, diabetes mellitus, previous stroke, transient ischemic attack, or thromboembolism (Markides & Schilling, 2003). CHA_2DS_2-VAS_C adds the components of vascular disease and sex. With the addition of vascular disease and sex to any patient with a score of at least 2 are recommended for anticoagulant therapy, granted they do not have any contraindications. The higher the $CHADS_2$ or CHA_2DS_2-VAS_C score, the higher the risk of stroke or other vascular disease (Gutierrez & Blanchard, 2016).

Although anticoagulant therapy has benefits of clot prevention, it also has the increased risk of causing unwanted bleeding. Patients who have a higher risk of bleeding are measured with ACC HAS-BLED clinical tool (Markides & Schilling, 2003). Hemorrhage risk is assessed using: hypertension, abnormal renal function and liver function, stroke, bleeding, labile INR, elderly, drugs and alcohol is used to confirm potential of hemorrhage (Gutierrez & Blanchard, 2016).

Anticoagulants and risks

Harter, Levine, & Henderson (2015) discussed how the coagulation cascade in the human body works and how anticoagulants can affect this cascade to provide medical treatment and regulation. Homeostatic regulations in the human body are balanced by thrombus or clot

formation and destruction. The human body achieves this balance through very complex interactions with platelets, the vascular endothelium, the coagulation cascade, and the fibrinolytic system. Estimates have shown that 65,000 patients are treated in United States emergency rooms annually for hemorrhages that are directly related to anticoagulant therapy (Harter, Levine, & Henderson, 2015). Safer anticoagulants have been sought in the medical field to help treat atrial fibrillation and to lessen the need for frequent monitoring and adjustment (Harter, Levine, & Henderson, 2015).

There are many forms of anticoagulants on the market today, all of which have different mechanisms of action on the coagulation cascade. The common denominator that all anticoagulants share is that they all have the risk of acute hemorrhage as their main adverse effect. Some anticoagulants require tighter control and monitoring, such as vitamin k antagonists or warfarin. Other medications do not need to be under as tight of control as warfarin such as the newer oral anticoagulants (NOACs), but in case of an emergent reversal of the medication due to a hemorrhagic bleed, warfarin is easily controlled and is easier to reverse than the NOACs (Harter, Levine, & Henderson, 2015).

Katritsis, Gersh & Camm (2015) presented findings on the current status of anticoagulant use for the treatment of a-fib, specifically use of non-vitamin K-dependent anticoagulants. Comparisons between different agents and warfarin were made and methods for assessment of anticoagulant activity and reversal were discussed as well.

Aspirin, an antiplatelet medication which prevents platelets from collecting at sites of injury in the patient's endothelium, was discussed in the study. Aspirin was shown to increase risk of stroke in patients over seventy-five years of age when used for anticoagulation of patients with a-fib (Katritsis, Gersh, & Camm, 2015). Clopidogrel, another antiplatelet drug, when

combined with aspirin displayed increased protection when combined rather than when either is used alone for stroke risk prevention (Katritsis, Gersh, & Camm, 2015).

When antiplatelet medication was compared to warfarin there was less protection overall with a relative risk of 1.44 for stroke, peripheral embolism, myocardial infarct, and vascular death (Katritsis, Gersh, & Camm, 2015). The Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA) echoed these findings and showed that warfarin is deemed a better choice regarding stroke, intracranial hemorrhage, or peripheral embolism risk when compared to aspirin in patients greater than 75 years, with a 52% reduced yearly risk of stroke, intracranial hemorrhage 1.8% and peripheral embolism 3.8% (Katritsis, Gersh, & Camm, 2015). Warfarin reduces the risk of stroke by approximately 60%, while antiplatelet agents like aspirin and clopidogrel have been shown to reduce the risk of stroke by only 20% (Katritsis, Gersh, & Camm, 2015). Warfarin seems to be the best choice in anticoagulant medication when compared to antiplatelet agents. Some drawbacks to warfarin include its narrow therapeutic range, many drug and food interactions; and it should be taken into consideration that the use of warfarin requires consistent blood monitoring via International normalized ratio or INR through physician visits and blood draws which can be costly to the patient over time (Katritsis, Gersh, & Camm, 2015). Patients who use warfarin and are very compliant were found to be within therapeutic range only 55% to 66% of the time (Gutierrez & Blanchard, 2016).

Due to the narrow therapeutic index of warfarin and the constant need of monitoring, newer anticoagulants were developed to give patients other options for blood clot prevention in a-fib. Factor Xa inhibitors, approved by the Food and Drug Administration or FDA, are another anticoagulant medication for non-valvular atrial fibrillation. The benefit of these drugs as compared to warfarin are the fixed dosing, lower interactions, and the eliminated need to monitor

INR (Katritsis, Gersh, & Camm, 2015). Factor Xa inhibitors are, however, more expensive as compared to warfarin, but they are the most affordable non-vitamin K oral anticoagulant. Reversal treatment from hemorrhage in emergent situations is difficult with factor Xa inhibitors due to the lack of antidotes and specific assays used to measure the anticoagulant effect (Katritsis, Gersh, & Camm, 2015).

Dabigatran, a direct thrombin inhibitor, is another form of anticoagulation that a patient can select. Dabigatran has been shown to be as effective as warfarin in stroke and embolus prevention with fewer intercranial bleeds 0.30% vs. 0.74% per year with number needed to treat equaling 227 (Gutierrez & Blanchard, 2016). Increased GI bleeding was more common in dabigatran as compared to warfarin showing 1.51% vs. 1.02% respectively per year, with the number need to harm equaling 204 (Gutierrez & Blanchard, 2016). Dyspepsia and stomach pain were found to be the most common side-effects of dabigatran as well as warfarin (Katritsis, Gersh, & Camm, 2015).

Watchman's Procedure

An alternative to using anticoagulation therapy for thromboembolism prevention is the Watchman LAA closure device. The Watchman device from Boston Scientific is the most extensively studied LAA occlusion device and is the only device approved by the FDA since March 2015 (Sharma, Park, & Lakkireddy, 2018). This device acts by occluding the LAA, preventing potential clots from entering systemic circulation. This treatment is beneficial since up to 90% of non-valvular atrial fibrillation strokes result from emboli that arise from the LAA. The device itself is made of a self-expanding nitinol frame with 10 fixation anchors to secure itself to the LAA. Between the frame is a fibrinic cap made from polyethyl terephthalate fabric which prevents the emboli from leaving the LAA (Möbius-Winkler et al., 2012). The device

comes in multiple sizes depending on the patient's anatomy, which is measured by ultrasound or computed tomography. The placement of the device requires minimally invasive surgery. The device is implanted by placing a qualified patient under general anesthesia. An incision is made at the femoral vein where catheter is introduced, and a guidewire is used to guide the watchman device in the necessary position through the atrial septum and over the left atrial appendage. Common complications of the procedure are pericardial effusions and stroke. Ultrasound and fluoroscopic imaging are used in conjunction with the placement of the device to assure there are no leaks or possible complications associated with the procedure (Möbius-Winkler et al., 2012). The Watchman device has been used since 2002 in Europe and 2003 in the US (Sharma, Park, & Lakkireddy, 2018).

After the procedure has been finished and the implanted device has been placed, the patient will be placed on warfarin and 81 mg of baby aspirin for at least 45 days as well as antibiotic prophylaxis for 6 months as recommended by the American Heart Association (Möbius-Winkler et al., 2012). It is important that patients stay on anticoagulants during the first 45 days post-implantation, as the epithelialization or cellular sealing of the Watchman device occurs and adheres fully to block the LAA. After 45 days have passed, echocardiogram is used to assess the epithelialization of the device as well as any clots or leaks, and the patient is taken off warfarin (Möbius-Winkler et al., 2012). The patient is then placed on aspirin and clopidogrel for 6 months (Sharma, Park, & Lakkireddy, 2018). After the six months, the patient is placed on aspirin indefinitely, however, some patients may need additional time for epithelialization of the device to prevent thrombus (Sharma, Park, & Lakkireddy, 2018). A prospective registry from 8 French centers with 469 patients with atrial fibrillation who underwent LAA closure, where 272

of them had the Watchman device, found a 7.2% device related occlusion per year over 13 months of follow up (Sharma, Park, & Lakkireddy, 2018).

Warfarin vs. Watchman

The PROTECT AF trial was made to compare systemic anticoagulation with warfarin in patients with a-fib to LAA closure via the Watchman device. The trial was a prospective, unblinded, randomized trial conducted at 59 centers in the United States and Europe (Reddy et al., 2013). Participants had to be equal to or greater than 18 years of age, with a history of paroxysmal, persistent, or permanent a-fib, eligibility of warfarin therapy, and with at least one additional stroke risk factor including age greater to or equal to 75, hypertension, diabetes mellitus, heart failure, prior stroke, transient cerebral ischemic attack, or systemic thromboembolism (Reddy et al., 2013). All patients were randomized in a 2:1 ratio to undergo Watchman implantation or to continue warfarin medication, establishing more focus on the Watchman procedure. Patients who were to undergo Watchman implantation received medications post-surgery and were to follow up with their provider for routine check-ups of the device placement. Eventually patients were taken off warfarin after stability and anatomic adherence of the Watchman device was confirmed. The control group received warfarin with an INR performed no less than every 2 weeks for 6 months and monthly thereafter to keep the INR between 2.0 and 3.0. Follow ups were scheduled at 45 days, 6, 9, and 12 months and twice annually after that. The purpose of the study was to determine whether LAA closure was not inferior to continued anticoagulation when taking in consideration all the possible adverse risks. Some of these risks include: hemorrhagic or ischemic strokes, unexplained deaths, and procedural events such as pericardial effusion which required intervention, procedure stroke, or device embolization, or major bleeding (Reddy et al., 2013).

Originally the PROTECT-AF trial had 707 randomized patients with nonvalvular atrial fibrillation that were selected including 463 who had the Watchman LAA, and 244 patients for warfarin therapy at a 2:1 ratio (Reddy et al., 2013). Out of all the participants, 15.3% and 22.5% in Watchman and warfarin groups respectively discontinued the study for various reasons (Reddy et. al., 2013).

Based on the results of the PROTECT-AF trial a follow up trial was performed. Holmes et. al (2014) summarized the follow up trial named PREVAIL. Overall, 407 patients who had a higher mean $CHADS_2$ score of greater or equal to 2 and were randomized in a 2:1 ratio just like the PROTECT AF. After 18 months, the composite of stroke, systemic embolism, and vascular or unexplained death was 0.064 in the Watchman group and 0.063 in the control group (RR 1.07, 95% CI: 0.57 to 1.89) which did not achieve the prespecified standard of noninferiority (Holmes et. al, 2014). The second coprimary efficacy endpoint of stroke or systemic embolism when Watchman was compared to Warfarin showed 0.0253 versus 0.0200 with a risk difference of 0.0053 (95% CI, -0.0190 to 0.0273) achieving noninferiority (Holmes et al., 2014). Procedure events were 2.2% in the population of study. Pericardial effusions were 0.4% (p=0.027) (Homes et al., 2014).

Reddy et al. (2017) focused on the PREVAIL trial as a part of a patient-level meta-analysis with the PROTECT-AF trial reporting the results of the patients 5 years after both trials were conducted. Together, both PREVAIL and PROTECT AF were combined for a total enrollment of 1,114 patients for 4,343 patient-years. Additionally, the composite endpoint via the meta-analysis was similar between groups (HR: 0.820; 95% CI: 0.58 to 1.17; (p = 0.27)) (Reddy et al., 2017). Systemic embolism was shown to be similar with both groups (HR: 0.961; 95% CI: 0.60 to 1.54 (p = 0.87)) (Reddy et al., 2017). LAA closure was superior in prevention of

hemorrhagic stroke (HR: 0.20, 95% CI: 0.07 to 0.56; (p = 0.0022) (Reddy et al., 2017). LAA also favored disabling or fatal stroke (HR = 0.45; 95% CI: 0.21 to 0.94; (p = 0.03)) (Reddy et al., 2017). Cardiovascular or unexplained death favored LAA as well (HR: 0.59; 95% CI: 0.37 to 0.94; p = 0.027) (Reddy et al. 2017).

Boersma et. al (2017) designed a study called EWOLUTION with a goal to assess the safety of left atrial appendage closure with Watchman in patients with or without contraindication to anticoagulation after one year. 1025 patients in 13 countries were scheduled for Watchman procedure and were selected and followed at 47 different centers pre and post procedure (Boersma et. al, 2017). Consecutive patient procedures at the corresponding facility was used to represent real-life practice and avoidance of selection bias was encouraged to the performing surgeons (Boersma et. al, 2017). The candidates all had CHA_2DS_2-VAS_c scores of 4.5 +/- 1.6; The mean age was 73.4 years +/- 9 years; transient ischemic attack or TIA or ischemic stroke was present in 312 and 155 patients respectively (Boersma et. al, 2017). 320 patients had a past hemorrhagic stroke and 750 were diagnosed as inappropriate for oral anticoagulation (Boersma et. al, 2017). The Watchman procedure was successful in 1005 patients and 1002 patients did not have a leak >5mm (Boersma et. al, 2017). Antiplatelet therapy was given to 784 patients, where vitamin K antagonists were used in 75 patients (Boerssma et. al, 2017). Thrombus was found in 28 patients during TEE follow up not correlated with drug regimen (p =.14); Ischemic stroke incidence was 1.1%, major bleeding rate was 2.6%, and out of most incidences (2.3%) were not related to procedure or device (Boersma et al., 2017).

NOACs vs. Watchman

Koifman et al. (2016) performed a MEDLINE search for studies which compared new oral anticoagulants or NOACs like apixaban, dabigatran, and rivaroxaban or Watchman's device

to warfarin therapy with recorded clinical results. A mixed treatment comparison model was used to directly and indirectly compare the three.

Overall, there were 14 studies which had 246,005 patients was included in the research. 124,823 were treated with warfarin, 120,450 were using NOACs, and the 732 remaining had the Watchman implanted (Koifman et al., 2016). The mean age of the study was 72 +/- 9 years, and the mean $CHADS_2$ score was 2.1 +/- 1.6. The results showed that NOACs (OR 0.46 CI 0.30-0.82) and Watchman (OR 0.21 CI 0.05-0.99) were superior to warfarin in hemorrhagic stroke prevention (Koifman et al., 2016). NOACs reduced total stroke (OR 0.78 CI 0.58-0.96) and major bleeding (OR 0.78 CI 0.65-0.91) when compared to warfarin (Koifman et al., 2016). An indirect comparison of Watchman's device and NOACs showed no considerable differences in the outcomes of patient care overall (Koifman et al., 2016). There was a higher likelihood of ischemic stroke with Watchman (OR 2.60 CI 0.60-13.96) as compared to NOACs (Koifman et al., 2016). There was a higher likelihood that patients would have a hemorrhagic stroke on NOACs as compared to Watchman's device (OR 0.44, CI 0.09-2.14) (Koifman et al., 2016). The conclusion of the study found that both NOAC and Watchman's device were superior to warfarin therapy (Koifman et al., 2016).

Cost Effectiveness

Reddy et al. (2018) performed an analysis to assess the cost-effectiveness of LAAC in comparison to warfarin and other NOACs. Some of the NOACs included dabigatran, apixaban and rivaroxaban in the prevention of stroke in nonvalvular a-fib in patients with a previous stroke or TIA (Reddy et al.,2018). A Markov model structure was made implementing data from a secondary prevention subgroup analyses of the non-vitamin K antagonist oral anticoagulant and LAAC pivotal trials (Reddy et al.,2018). The cost effectiveness model was conducted from a US

Medicare perspective over a 20-year span. 10,000 patients aged 70 years with a CHA_sDS_2-VAS_c score of 7 and HAS-BLED score of 3 was used (Reddy et al.,2018).. The conclusions of the test showed that the initial payment of LAAC is higher than warfarin or NOAC initially, however at 10 years LAAC has more quality-adjusted life years with lower totaling costs (Reddy et al.,2018). LAAC was shown to be the most cost-effective treatment strategy for prevention of stroke in a-fib (Reddy et al.,2018).

Another study cost-effectiveness model that was done by Reddy et. al (2016) focusing on patients who had contraindications to warfarin. Data from 3 studies on stroke prevention were used in a cost-effectiveness model (Reddy et al., 2016). The Watchman device, aspirin and clopidogrel and apixaban were evaluated. The analysis was made from a German healthcare payer prospective over 20 years (Reddy et. al, 2016). The results of the study showed that the Watchman device is a cost-effective/saving device in patient with non-valvular a-fib who are at high risk for stroke but have absolute contraindications to warfarin (Reddy et. al 2016).

McKeown (2015) wrote an article wrote an article summarizing a study done in 2015 which showed the 4-year clinical events, rates of stroke, quality of life data from the PROTECT AF trial (McKeown, 2015).

"When compared over a lifetime, [LAA closure] proved to be the most cost-effective treatment," said Vivek Y. Reddy, MD, of Mount Sinai Medical Center (McKeown, 2015).

Comparison of Therapies for Nonvalvular A-Fib

	Total Costs	Total QALYs
5 Years		
LAA Closure	$20,892	3.455
Warfarin	$10,764	3.387
NOACs	$20,924	3.448
10 Years		
LAA Closure	$25,425	5.855
Warfarin	$26,834	5.601
NOACs	$39,260	5.751
15 Years		
LAA Closure	$29,075	7.309
Warfarin	$41,326	6.843
NOACs	$53,431	7.077
20 Years		
LAA Closure	$31,198	8.031
Warfarin	$49,946	7.392
NOACs	$61,701	7.682

Figure 1. Graph comparing costs of different anticoagulation therapies in nonvalvular A-Fib: Value 2015-2019. Reprinted from *Study Affirms Cost-Effectiveness of Watchman LAA Closure Device for Stroke Reduction*, by tctMD/the heart beat, December 14,2015 retrieved from https://www.tctmd.com/news/study-affirms-cost-effectiveness-watchman-laa-closure-device-stroke-reduction/ Copyright June, 2018

Figure 1 shows the estimated monetary costs of left atrial appendage closure compared to long term warfarin use and novel oral anticoagulants during 2015. LAA proves to be the most cost effective over a lifetime (McKeown, 2015). Overall, LAA closure was more expensive the first year of treatment and had lower quality-adjusted life years (McKeown, 2015). By years 5,7, and 10, LAA was more cost effective and had more quality-associated life years than both warfarin and novel oral anticoagulants (McKeown 2015). Centers of Medicaid and Medicare, based on this data, would be favorable for coverage of LAA closure procedures (McKeown, 2015).

Discussion

Anticoagulation therapy and Watchman's device have been discussed at length in the literature review. Both serve as beneficial prophylactic treatments in preventing blood clots, however, both also have significant risks involved with their implementation when it comes to a-fib. Anticoagulants run the risk of potential hemorrhage, whereas Watchman's device mainly shows issues with both pre and post-surgical placement. Regardless of the risks of surgery, Watchman's procedure, in the author's opinion, shows less risk and less cost in the short term as well as the long term than treatment with anticoagulants.

For prevention of embolus formation from atrial fibrillation in the adult and older adult population, would anticoagulant therapy or Watchman procedure be a better choice?

Both anticoagulant therapy and Watchman's procedure are currently offered and used in clinical practice today. Anticoagulation therapy has been a mainstay for years in the medical industry while Watchman's device has only been implemented since 2002.

Eligible patients for both procedures must be assessed by their cardiologist before considering either therapy. According to Harter, Levine, & Henderson, (2015) anticoagulation therapy has been improved upon since the use of only vitamin K antagonists such as Warfarin. The improvements include decreased monitoring, risk of bleed, as well as interaction with other medications or food. Warfarin, on the other hand requires constant checking and measurements via physician visits as well as attention to the intake of certain foods. Although the prophylactic treatment has gotten much better with the development of NOACs, acute hemorrhage still is the most feared adverse event faced when using any anticoagulants, which has an increase in morbidity and mortality (Harter, Levine, & Henderson, 2015).

Watchman's procedure, a viable alternative to anticoagulants has its own risks as well. Watchman's procedure has shown both pre- and post-operative risks, including air embolism, anesthesia risks, thrombosis, pericardial effusion, and stroke (Mobius-Winkler et al., 2012). The discussion that follows summarizes the findings in the literature review.

Eng and Saw (2016) reported the comparison of the Watchman's procedure and anticoagulation therapy with the PROTECT-AF trial. Eng & Saw (2016) summarized the study initially and the follow-ups that ensued.

> "At the initial 1,065 patient-years of follow-up, primary efficacy end point of stroke, systemic embolism, and cardiovascular death in patients implanted with Watchman was non-inferior to stroke prevention compared to the control cohort (3 vs. 4.9 events per 100 patient-years; risk ratio or RR = 0.62 CI, 0.35-1.25) "(Eng & Saw 2016).

The Watchman group did demonstrate more safety events, most likely due to the invasive nature of the procedure, around 5.5% per year (95% CI, 4.2%-7.1% per year) than the warfarin group: 3.6% per year (95% CI, 2.2%-5.3% per year, RR 1.53) (Eng & Saw 2016).

> "After the initial study, a longer-term follow-up of 3.8 +/- 1.7 years showed the primary efficacy event rates were 2.3 per 100 patient years, (95% CI, 1.7-.2) with Watchman and 3.8 per 100 patient years (95% CI, 2.5-4.9) with warfarin "(Eng & Saw, 2016).

Superiority and non-inferiority of Watchman as compared to warfarin was shown. With the Watchman device there was a 40% risk reduction (RR = 0.6; 95% CI, 0.41-1.05) of all cause stroke, systemic embolism, cardiovascular and unexplained death. Hemorrhagic stroke was reduced by 85% (RR =0.15, 95% CI, 0.15-1.00); there was a 63% reduction in disabling stroke, (RR = 0.37, 95% CI, 0.15-1.00), 60% reduction in cardiovascular death, (RR=0.4; 95% CI, 0.23-

0.82), and 34% decrease in all-cause mortality, (RR = 0.66, 95% CI, 0.45-0.98) (Eng & Saw, 2016).

The PREVAIL trial, which followed up the PROTECT-AP trial showed there was decrease from 8.7% of post procedural complication to 4.2% complication (p=0.004) according to Sharma, Park, & Lakkireddy (2018). There was also established non-inferiority of Watchman's device compared to warfarin therapy in the PREVAIL trial as shown in the PROTECT-AP trial (Sharma, Park, & Lakkireddy, 2018). Based on the PREVAIL trial, it can be argued that lack of experience and/or training of surgeons performing the Watchman's implantation resulted in more safety events that happened in the PROTECT-AF trial (Sharma, Park, & Lakkireddy, 2018). To date, reported rates of procedure-related complications have been low since FDA approval of Watchman device implantation (Sharma, Park, & Lakkireddy, 2018). After the post-FDA approval in the United States, 3,822 consecutive patients had the Watchman device procedure performed by 382 physicians. Procedure success rates measured 95.6% and complication rates for conditions such as pericardial tamponade, procedure related stroke, and mortality rates totaled 1%, 0.08%, and 0.08% respectively (Sharma, Park, & Lakkireddy, 2018).

Reddy et al. (2017) used the previous PREVAIL and PROTECT-AP trial as stated in the literature review as a part of a patient-level meta-analysis reporting the results of the patients approximately 5 years after both trials were conducted. The article used Bayesian model of statistics which means that the data gathered on the study could determine the outlook of the procedure and their complications, comorbidities, mortality. The results of the test showed that LAAC with Watchman provides stroke prevention in patients without valvular AF comparable to warfarin, while also providing reductions in major bleeding (Reddy et al. 2017).

Boersma et al., (2017) discussed the EWOLUTION study, which showed that the Watchman procedure had a high success rate, and stroke risk reduction related to the procedure as compared to its earlier studies was effective. The EWOLUTION study, at the time, was the largest prospective real-world registry on Watchman device and the only study reporting on 1-year follow ups on the procedure outcomes to date. This study was very informative and did a good job comparing Watchman procedure with the risks, adverse effects, and efficacy especially in comparison to anticoagulant therapy. The patient population selected was beneficial to study due to the advanced age and multiple comorbidities, the patients all had CHA_2DS_2-VAS_c scores of 4.5 +/- 1.6 and the mean age was 73.4 years +/- 9 years (Boersma et al.,2017). The increased age as well as the multiple co-morbidities displayed potential future candidates who suffer from many disorders/diseases that could possibly be interested in the Watchman procedure. It should be noted that Boston Scientific paid the performing physicians of this study for expenses both pertaining to and outside of the study. This raises some concern since Boston Scientific is the main manufacturer of the Watchman device, which can cause some bias from the researchers. With that said, there are very few if any other leading Watchman device manufacturers in the world. The EWOLUTION study had benefited in having 13 different countries and multiple centers showing a 'real world' view of Watchman therapy. Some negatives of the study showed that the post procedural antithrombotic regimen was not taken consistently amongst some of the patients, as well as the follow up in performing TEE or CT to assess and confirm epithelialization and whether there were leaks around the device (Boersma et al., 2017). 13% of the patients did not follow up for imaging which affected the absolute numbers overall (Boersma et al., 2017). Additionally, lack of detailed information on patients participating in the study was shown as well. Overall, this article was one of the strongest statistical studies done to date, which

reinforces the notion that Watchman procedure should be heavily considered in patients who are on anticoagulants or are contraindicated to anticoagulants who would like to try LAAC procedure instead (Boersma et al., 2017).

Unfortunately, there are very few studies that compare Watchman's device to NOACs. Koifman et al. (2016) used the MEDLINE search to compare NOACs and Watchman's device to warfarin. Both NOACs and Watchman's device were shown to be were superior to warfarin in hemorrhagic stroke prevention (Koifman et al., 2016). For the indirect comparison of NOACs and Watchman's device showed no considerable differences in the outcomes of patient care overall (Koifman et al., 2016), NOACs had a higher rate of hemorrhagic stroke (OR 0.44, CI 0.09-2.14) compared to Watchman's device (Koifman et al., 2016). While Watchman's device had a higher occurrence of ischemic stroke (OR 2.60 CI 0.60-13.96) as compared to NOACs (Koifman et al., 2016). Ischemic strokes which may or may not happen after LAAC via Watchman have been shown to be non-disabling and result in functional independence overall as compared to hemorrhagic stroke (Reddy et al., 2016). More long-term data as well as head to head studies need to be performed to fully assess the efficacy and safety of Watchman's device compared to anticoagulants are needed (Reddy et al., 2018).

When comparing Watchman's procedure and long-term anti-coagulant therapy for eligible patients, which choice would be the best economically for the patient?

As stated in the Literature Review, Reddy et al. (2018) built a Markov model using the data from different subgroups in preventing blood clots in a-fib. The results of the analyses showed that Watchman's device had cost effectiveness 5 years post procedure compared to dabigatran, and warfarin and apixaban at year 6 (Reddy et al., 2018). By the time 10 years went by, Watchman's procedure had more quality-adjusted life years and lower costs, with a mean

average of $14, 087.75 compared to all other treatments in the study: warfarin, dabigatran, apixaban, and rivaroxaban (Reddy et al., 2018). Overall, it was shown that LAAC was superior regarding cost effective treatment and prevention of stroke in atrial fibrillation (Reddy et al., 2018). To note, there is not a randomized controlled trial to evaluate all comparisons e.g. Watchman's device, warfarin, NOACs, etc. to each other (Reddy et al., 2018). There is also limited literature on secondary prevention in patients with a-fib (Reddy et al., 2018). Another limitation to this study was that data was extrapolated out to 20 years via US healthcare systems and costs, not being true to real-world clinical practice (Reddy et al., 2018).

Reddy et. al (2016) also created the cost effectiveness model of Watchman device with absolute contraindications to warfarin. The results of the study showed more quality of life years when LAAC was compared to aspirin 1.45 vs 1.44 and apixaban 2.65 vs. 2.64 at 2 and 4 years. LAAC was cost saving compared to aspirin at 7 years and apixaban at 8 years. By 10 years, LAAC was 25 % less expensive than aspirin and 15% less expensive than apixaban while providing 0.6 additional quality of life years compared to 0.2 years in aspirin and apixaban (Reddy et al., 2016). The limitations of this study were that it only allowed one clinical event for every 3-month cycle as well as hypothesizing data based on assumed patterns of cost (Reddy et al., 2016). This model only focuses on the German healthcare system and costs which may not reflect other healthcare systems globally (Reddy et al., 2016). Overall, the LAAC via Watchman device can change the way patients with atrial fibrillation are managed at risk for both stroke and bleeding (Reddy et al., 2016). The study overall shows that the Watchman device is safe and effective for treatment as well as cost-effective over the long term (Reddy et al., 2016). Even though extrapolation was used, I believe that this study was useful regarding cost effectiveness of Watchman as compared to aspirin therapy or apixaban (Reddy et al., 2016). Unfortunately,

some patients cannot afford their medicines, but with LAAC via Watchman implantation non-adherence is not possible. When Warfarin and NOAC are compared with LAAC it is obvious that the cost of the procedure is relatively high due to the cost of the procedure itself and potential complications, however, cost is minimal over time due to no other follow up payments being made (Reddy et al., 2016).

Overall, the data based above shows a positive outlook on costs and quality of life years when Watchman's device is taken into consideration in long term treatment and prevention of a-fib related embolus.

Applicability to Clinical Practice

It should be stated that neither warfarin, non-oral anticoagulants, nor Watchman device can completely abolish strokes in patient with atrial fibrillation (Reddy et al. 2017). It is the author's goal that at the end of this scholarly project that the reader albeit a clinician, patient, or someone who has an interest in medicine takes away the benefit that Watchman's procedure has compared to long term anticoagulation treatment. The decreased rate of bleeding, hemorrhagic stroke, the non-inferiority to anticoagulants specifically warfarin, and ease of compliance are all benefits that the patient must be educated on when considering whether to undergo the Watchman's procedure as with every surgery, there is a risk of complications including bleeding, infection, nerve damage, et. In the case of Watchman's procedure risks include pericardial effusions, which is most commonly caused by operator (Möbius-Winkler et al., 2012). Since the implementation of the Watchman's procedure and as more surgeons gain experience and technology improves, these risks have been shown to be on the decline (Reddy et al. 2017). As mentioned in the Discussion, as well as the articles referenced for this paper more randomized control trials are needed to directly compare anticoagulants, specifically NOACs to Watchman's device to fully encompass efficacy vs. adverse effects. With that said, clinicians should be encouraged at how far Watchman's device has come and how it continues to be studied, tested, and improved upon. It is the hope of the author that if a clinician does have a patient who suffers from atrial fibrillation and is currently treated with an anticoagulant for long term prophylaxis, Watchman's procedure should be thought of and mentioned to the patient giving them a potentially better prophylactic and cost-effective treatment.

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